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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,818	10/30/2000	Brian L. Ganz		7165

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EXAMINER	
GORDON, BRIAN R	

ART UNIT	PAPER NUMBER
1743	8

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,818	GANZ ET AL.	
	Examiner	Art Unit	
	Brian R. Gordon	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed September 2, 2003 with respect to claims 1-37 have been considered but are moot in view of the new ground(s) of rejection.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-5 and 32-36, 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marousiss et al. US 2001/0048899.

Marouiss discloses an integrated sample-processing system and components for preparing and/or analyzing samples. The components may include a transport module, a fluidics module, and an analysis module, among others.

The processing of such samples has been facilitated by packaging samples in high-density sample holders, such as microplates, for analysis together in an automated device. FIG. 1 shows an offset **stack of microplates,** illustrating the range in possible well densities and well dimensions. Plate 130 has 96 sample wells. Plate 132 has 384 wells. Plate 134 has 1536 wells. Plate 136 has 3456 wells. Plate 138 has 9600 wells.

FIG. 2 is a perspective view of a system 500 for preparing and/or analyzing samples. System 500 includes at least one input/output (I/O) site 502 for sample input and output, and a plurality of function modules (or stations) for performing a plurality of functions, including **a transport module** 504 (indexing device), a fluidics module 506, and an analysis module 508. The transport module participates in sample transport, for example, by shuttling a sample or sample holder between the I/O sites, fluidics module, and analysis module. **The fluidics module participates in sample preparation, for example, by adding (and/or removing)** (solution removal area) **a component of a sample to a sample holder.** The analysis module participates in sample analysis, for example, by **performing an optical analysis** of a sample based on photoluminescence, chemiluminescence, absorbance, and scattering, among others. The components of system 500 may be configured to enhance function, convenience, and/or appearance.

FIG. 4 is a schematic view of a generalized system 700 for preparing and/or analyzing samples. System 700 includes at least one I/O site 702 and a plurality of function modules, including a transport module 704, a fluidics module 706, and an analysis module 708, as above, as well as N auxiliary modules 710 associated with redundant and/or additional functionalities, such as cleaning, sealing, storage, sample preparation, etc. Here, N may range from zero to several or more. A cleaning module might include components for emptying and/or cleaning sample holders. A sealing module might include components for sealing, unsealing, and/or otherwise covering and uncovering sample holders (lid lifter). An incubation module might include components

for incubating sample holders and their associated samples, with environmental control of atmosphere, temperature, agitation, and so on. A sample preparation module might include components for particular sample-preparation functions, such as a thermocycler for performing heating and cooling during the polymerase chain reaction (PCR).

Function modules generally include one or more function sites at which a corresponding function is performed. For example, a fluidics module may include a **dispense site 712** at which a fluid is dispensed, an analysis module may include an examination ("exam") site 714 at which a sample is analyzed, and an auxiliary module may include an auxiliary site 716 at which an auxiliary function is performed, such as cleaning, sealing, storage, etc. A transport module may be connected directly or indirectly with I/O sites 702 for sample input and output, and with one or more of the function sites. If the transport module is connected indirectly to a function (or I/O) site, the transport module might hand off a sample holder at a transfer site to a separate transport mechanism associated with the respective function module. A transport module also may be connected to additional **robotics for providing and removing sample holders from the I/O sites.**

Sample holders may be used alone, in stacks, or in combination **with seals or covers.** Sample holders may support samples at low, intermediate, or high density, and be designed for single or multiple use.

The transport module may employ a variety of singulation strategies, depending in part on the number of I/O sites, the nature of the I/O sites (i.e., input, output, or both), and the location in the stack from which plates are taken and/or added (typically bottom

and/or top). Transport module 2100 has two I/O sites, from which plates are taken and/or added at the bottom. Typically, but not necessarily, one of these sites is dedicated to input, and the other is dedicated to output. To input a plate, a robot (1) removes a plate from the bottom of an input stack of plates at the input site, (2) transports the plate to the transfer site, and (3) transfers the plate at the transfer site to a transport mechanism for an associated function module. To output a plate, the robot (1) takes the plate from the transport mechanism for the function module at the transfer site, (2) transports the plate to the output site, and (3) transfers the plate at the output site to the bottom of an output stack of plates at the output site. In transport module 2100, these functions are performed by the intersite and intrasite drivers, with preferred throughputs ranging from about 1 second per plate to about 5 seconds per plate.

The first input step (Panel A) comprises **raising lifters 2234 to elevate a stack 2230 of plates 2232a,b** through contact of the plates with an upper surface 2240 of the lifters and to push latches 2204 into a retracted position through contact of the latches with a side surface 2242 of the lifters. In the depicted embodiment, the lifters are raised from their resting height to their maximum height (about 5 mm), after which electromagnets 2212 behind each latch are energized to hold the latch in the retracted position. In other embodiments, the latches may be moved to and/or held in the retracted position at alternative times and/or by alternative mechanisms, such as a solenoid-actuated pin. If it is unnecessary to reverse the function of the latch (for example, because the latch is used only for input), the latch may be held in the retracted

position by eliminating a notch 2244 in the lifter that otherwise permits the pick portion of the latch to move under the plates.

Lift platform 2302 includes a base 2306 and sets of lifters 2308a,b corresponding to each I/O and/or function site. The lifters generally comprise any mechanism configured to raise or lower a plate in cooperation with a singulation mechanism. Lifters 2308a for use in the I/O sites are substantially rectangular and include a top notch 2310 for interaction with a latch, as described above. Lifters 2308b for use in the function site are substantially cylindrical and may be used to raise and lower a plate for transfer to a transport mechanism.

The I/O sites in the transport module may accommodate a variety of commercially available plates (e.g., microplates) and are large enough so that the plates can be placed in the sites by a robot or a human hand. Moreover, as shown in FIG. 3, the I/O sites also may accommodate a variety of commercially available **pre- and postprocessing plate bins (or magazines) for holding a stack of plates before and after analysis**, respectively. A preprocessing bin may be removed from an I/O site and replaced with another preprocessing bin containing a new stack of plates with samples to be analyzed. Similarly, a postprocessing bin may be removed from an I/O site and replaced with another postprocessing bin to receive a new stack of plates with samples that have been analyzed. The plate bins can be used with other robotics (such as an appropriate combination of function modules) to dispense, wash, and read without restacking plates. Preferred plate bins typically accommodate zero to sixty plates.

Morouiss et al. does not specifically recite that the device comprises a slide positioning element, however it is disclosed that the device comprises an element for positioning microplates in a position to receive fluid dispensed from the dispensing modules. It would have been obvious to one of ordinary skill in the art at the time of the invention to recognize that slides may incorporated in the device as targets for the samples to be dispensed for analysis.

5. Claims 6-15, 17-19, 21-24, 26-27, 29, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marouiss et al. as applied to claims 1-5 and 32-36, 38-41 above, and further in view of Little US 6,024,925 and Palcic et al. US 6,026,174.

Marouiss et al. do not disclose that the substrate is a slide or that the device further comprises a light source and a camera.

Little et al. discloses parallel dispensing tools that can deliver defined and controlled volumes of fluid to generate multi-element arrays of sample material on a substrate surface. The substrates surfaces can be flat (slides) or geometrically altered to include wells of receiving material. FIG. 1 depicts a system 10 that includes a data processor 12, a motion controller 14, a robotic arm assembly 16, a monitor element 18A, a central processing unit 18B, a microliter plate of source material 20, a stage housing 22, a robotic arm 24, a stage 26 (isolated base), a pressure controller 28, a conduit 30, a mounting assembly 32, a pin assembly 38 (dispense head), and substrate elements 34. The interior chamber can be connected to a pressure source that will control the pressure within the interior chamber to regulate the flow of fluid

within the interior chamber of the pins. In the view shown by FIG. 1, it is also illustrated that the robotic assembly 16 can include a moveable mount element 40 and a horizontal slide groove 42. The robotic arm 24 can optionally pivot about a pin 36 to increase the travel range of the arm 24 so that arm 24 can dispose the pin assembly 38 above the source plate 20. The data processor 12 depicted in FIG. 1 can be a conventional digital data processing system such as an IBM PC compatible computer system that is suitable for processing data and for executing program instructions that will provide information for controlling the movement and operation of the robotic assembly 16. It will be apparent to one skilled in the art that the data processor unit 12 can be any type of system suitable for processing a program of instructions signals that will operate the robotic assembly 16. Optionally the data processor 12 can be a micro-controlled assembly that is integrated into the robotic housing 16. In further alternative embodiments, the system 10 need not be programmable and can be a single board computer having a firmware memory for storing instructions for operating the robotic assembly 16. In the embodiment depicted in FIG. 1, there is a controller 14 that electronically couples between the data processor 12 and the robotic assembly 16. The depicted controller 14 is a motion controller that drives the motor elements of the robotic assembly 16 for positioning the robotic arm 24 at a selected location. Additionally, the controller 14 can provide instructions to the robotic assembly 16 to direct the pressure controller 28 to control the volume of fluid ejected from the individual pin elements of the depicted pin assembly 38. The depicted robotic assembly 16 is a gantry system that includes an XY table for moving the robotic arm

about an XY plane, and further includes a Z axis actuator (linear actuators) for moving the robotic arm orthogonally to that XY plane.

FIG. 6A is a piezo electric transducer element which forms around the parameter of the capillary 112 and can transform an electrical pulse received from the pulse generator within a robotic assembly 16 to cause fluid to eject from the orifice 118 of the capillary 112.

After depositing the sample arrays onto the surface of the substrate, the arrays can be analyzed using any of a variety of means (e.g., spectrometric techniques, such as UV/IVIS, IR, fluorescence, chemiluminescence, NMR spectroscopy or mass spectrometry).

The matrix drops were observed by employing visualization via a CCD camera (column 16, lines 56-65).

It is also revealed that a windows based control software maybe employed as well as a strobe light is used to illuminate the tip of the dispenser in order for a camera to be employed to check the integrity and cleanliness of the tip.

Although Little does not mention that the substrate is a slide, it would have been obvious to one of the ordinary skill in the art to recognize that the flat substrate could be a slide. Furthermore it would have been also obvious to ordinary skill in the art modify the device of Marouiss et al. to include the flat surface (slide) of Little to which sample arrays are dispensed to for identifying the presence of biomolecules (such as DNA) and their characteristics. It would have also been obvious to employ the use of the camera and strobe light of Little to check the cleanliness of the

dispense head.

Although Marouiss et al. in view of Little recites that a CCD Camera may be employed for visualization, it is not specifically recited that the camera supplies image data to a computer for analysis.

However, Palcic et al. US 6,026,174 discloses a system and method for automatically detecting diagnostic cells and cells having malignancy-associated changes (MAC).

The MAC detection system according to the present invention is shown in FIG. 1. The system 10 includes a digital microscope 12 that is controlled by and interfaced with a computer system 30. The microscope 12 preferably has a digital CCD camera 14 employing a scientific CCD having square pixels of approximately 0.3 mm by 0.3 mm size. The scientific CCD has a 100% fill factor and at least a 256 gray level resolution. The CCD camera is preferably mounted in the primary image plane of a planar objective lens 22 of the microscope 12. A stable light source 18, preferably with feedback control, illuminates the cell sample while an image of the slide is being captured by the CCD camera. The lens 22 placed between the sample 16 and the CCD camera 14 is preferably a 2x/0.75 objective that provides a depth of field in the range of 1-2 mm that yields a distortion-free image.

The images produced by the CCD camera are received by an image processing board 32 that serves as the interface between the digital camera 14 and the computer system 30. The digital images are stored in the image processing board and manipulated to facilitate the detection of MACs. The image processing board

creates a set of analog video signals from the digital image and feeds the video signals to an image monitor 36 in order to display an image of the objects viewed by the microscope.

An image of a frame from the slide is captured by the CCD camera and is transferred into the image processor. In this process, the CCD sensor within the camera cleared and a shutter of the camera is opened for a fixed period that is dependent on the intensity of the light source 18. After the image is optimized according to the steps described below, the stage then moves to a new position on the slide such that another image of the new frame can be captured by the camera and transferred into the computer memory. Because the cell sample on the slide occupies a much greater area than the area viewed by the microscope, a number of slide images are used to determine whether the sample is MAC-positive or negative. The position of each captured image on the slide is recorded in the computer system so that the objects of interest in the image can be found on the slide if desired.

Once an image from the slide is captured by the CCD camera and stored in the image processing board, the computer system determines whether the image produced by the CCD camera is devoid of objects. This is performed by scanning the digital image for dark pixels. If the number of dark pixels, i.e., those pixels having an intensity of the background intensity minus a predetermined offset value, is fewer than a predetermined minimum, the computer system assumes that the image is blank and the microscope stage is moved to a new position at step 60 and a new image is captured at step 54.

It would have been obvious to one of ordinary skill in the art to modify the modified the modified device of Marouiss to allow for subsequent analysis of the deposited sample arrays in order to determine the presence of biological organisms and their characteristics. It would have also been obvious to use the camera of Little as employed by the method of Palcic and using the CCD camera present as an additional form or means of analysis (additional to e.g., spectrometric techniques, such as UV/IVIS, IR, fluorescence, chemiluminescence, NMR spectroscopy or mass spectrometry) for the samples deposited on the substrate.

As to claims 7-15 and 19, the examiner hereby submits that the claims are not structural limitations of the device but are moreso directed to the capability of the device and the data transmitted from the camera to the computer. The modified device of Marouiss is capable of performing in the manner recited in those claims.

As to claim 24, it would have also been obvious to provide the array on a vibration isolated base when one is attempting to dispense a precise volume of fluid when required.

6. Claims 16, 20, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marouiss in view of Little and Palcic as applied to claims 6-15, 17-19, 21-24, 26-27, 29, and 37 above, ~~and further in view~~ of and further in view of Ridgeway et al. US 5,879,628.

Marouiss in view of Little and Palcic does not disclose that a 2D bar code is used for identification of information.

Ridgeway discloses a device for handling samples in which a CPU maybe employed to control all operations. A bar code is also provided for containing information that is related to the reagents. The information can also be entered by way of a touch screen in conjunction with the keyboard. The device also employs the use of a rinsing station for flushing the inside and outside of the needle of the syringe system.

It would have been obvious to one of the ordinary skill to modify the modified device of Marouiss by employing the teachings of Ridgeway to include a washing station to allow for the reduction of cross-contamination and a bar code to store the related about the assay slide. As to the vacuum manifold, it would have been obvious to use a vacuum manifold as the pressure source for aspirating and dispensing the reagents for the array.

7. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marouiss et al. in view of Little and Palcic et al. as applied to claim claims 6-15, 17-19, 21-24, 26-27, 29, and 37 above, and further in view of Overbeck.

Marouiss et al. in view of Little and Palcic et al. does not disclose the use of quill type dispensers.

Overbeck discloses a fluid deposit assembly in which piezo and quill type dispensers are used to jet small volumes of fluid to a substrate.

It would have been obvious to one of the ordinary skill in the art at the time of the invention to modify the modified device of ~~Little~~ Marouiss et al by employing the teachings of Overbeck for quill and piezo dispensers are capable of depositing very small volumes of fluid as

well as the employment of quill tips allows one to suck up a desired amount of fluid (column 2 lines 8-18).

Conclusion

8. No claims allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Velghe et al., Williams et al., Hamel et al., Stylli et al. (,611 and ,218), Shtrahman et al. disclose sample processing devices that comprise stacking or storage elements.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Gordon whose telephone number is (703) 305-0399. The examiner can normally be reached on M-F, with 2nd and 4th F off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 703-308-4037. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

brg
November 6, 2003

Maureen M. Wallenhorst
MAUREEN M. WALLENHORST
PRIMARY EXAMINER
GROUP [redacted] 1700